

Statements under 37 C.F.R. §1.173(c)

The following statements are made pursuant to the requirements of 37 C.F.R. §1.173(c). Patent claims 1-4 have been cancelled without prejudice toward the continuation of prosecution in a continuing application. Added claims 5-176 and 178-209 have also been cancelled without prejudice. Claims 177 and 210-228 are the only claims now pending in the case.

Pursuant to 37 C.F.R. §1.173(c), the following is an explanation of the support in the disclosure of the patent for the changes made to the claims by the present amendment.

Claims 210-214 have been amended to define the extent to which the aggregation of β -amyloid is inhibited or the solubility of soluble β -amyloid is maintained. Thus the phrase "inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid," wherever it appears in the claims, has been amended to read -- inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33--. The underlined portion was added.

The concept of use of an antibody that inhibits aggregation or that maintains the solubility of β -amyloid to an extent at least as great as that obtainable with antibody AMY-33 is supported by the present specification. For example, reference is made to column 6, lines 21-26, where it states:

In the preferred embodiment the human monoclonal antibody that binds to an aggregating protein and which prevents aggregation is utilized. If a further preferred embodiment the monoclonal antibody is an anti- β -amyloid and is designated AMY-33 which recognizes amino acids 1-28 of β -amyloid.

Thus, the generic idea of using an antibody that prevents aggregation is presented as is the specific idea of using antibody AMY-33. As the genus of an antibody which has any amount of aggregation and the species of an antibody that has the same amount of aggregation as AMY-33 are both supported, the concept of use of an antibody within the range of the amount of inhibition achieved by AMY-33 and up is supported. Note also the present specification at column 16, lines 15-21 where it states:

On the basis of applicant's findings regarding other antigen-antibody systems studies ..., the formation of the immunocomplexes with selected, highly specific monoclonal antibodies, should provide a general and convenient method to prevent aggregation of the proteins ...

Thus, it is clear that the present invention is directed to the use of "selected, highly specific monoclonal antibodies." An example of highly specific monoclonal antibody given is AMY-33. Thus, this further supports the use of any selected highly specific monoclonal antibody which inhibits aggregation at least to the extent of AMY-33. Note, for example, *In re Anderson*, 176 USPQ 331, 336 (CCPA 1973) where the court reversed a rejection based on lack of support

for an amendment changing the terminology "containing a medicament" to "carrying a medicament," reasoning:

The question, as we view it, is not whether "carrying" was a word *used* in the specification as filed but whether there is *support* in the specification for employment of the term in a claim; is the concept of carrying is present in the original disclosure? We think it is.
[emphasis original]

Similarly, here the concept of the use of antibodies that inhibit the aggregation of β -amyloid at least to the extent that AMY-33 does so is found in the specification and thus the claim language is supported.

Claims 210, 211 and 214 have been amended to delete "or recognizes an epitope within residues 1-28 of beta-amyloid." In each of these claims, the deleted portion was part of an alternative and the first part of the alternative remains unchanged. Thus, just as the claiming "antibody A or antibody B" fully supports an amendment to specific only "antibody A," so removal of the alternative phrase here does not change the support for the remainder of the claim.

New claims 215-218 are identical to claims 210, 211, 177 and 214, respectively, except that they specifically claim the second of the alternatives in paragraph (ii) that previously appeared in these claims but were deleted from these claims by the present amendment. Thus, claims 215-218 specify that a monoclonal antibody is selected that "(ii) recognizes an epitope within residues 1-28 of beta-amyloid."

Thus, these claims are supported for the same reasons that claims 210, 211, 177 and 214 were previously supported. Effectively, the previous claims were drawn to species A or B. Now applicant has opted to insert two independent claims, one to species A and one to species B. Each of the present species claims are supported for the same reasons that the previous claims to species A or B were previously supported.

Claims 219-224 are identical to claims 210, 211, 177 and 212-214, and claims 225-228 are identical to claims 219-221 and 224, except that there is a change in subparagraph (i) of the independent claims. The claims previously read that the monoclonal antibody "inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33." This phrase has now been changed so as to read "disaggregates an aggregate of beta-amyloid." The "disaggregating" language appeared in the claims of the present application until applicant's amendment of February 23, 2004, in which this language was deleted. However, its deletion was not required by any of the rejections of record. Support for the requirement of the antibody or fragment as being effective to disaggregate an aggregate of β -amyloid may be found, for example, in the paragraph beginning column 5, line 23, and the sentence beginning at column 5, line 40.

Claim 210 has further been amended to add at the end "and wherein said antibody or fragment is not conjugated with a detectable moiety." This language is supported at column

11, at the paragraph beginning on line 52, where it states that the monoclonal antibody of the invention "can be bound to a solid support substrate or conjugated with a detectable moiety." It further states:

The detectable moieties contemplated with the present invention can include, but are not limited to, fluorescent, metallic, enzymatic and radioactive markers

In view of the disclosure that the present application may include such markers, it is not new matter to add to the claim that the antibodies exclude such markers. In other words, this is an option that the specification indicates can be present or not and the present claims now specify the antibodies without that option.

REMARKS

Claims 177 and 210-228 presently appear in this case. No claims have been allowed. The official action of March 23, 2009, has now been carefully studied.

Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a therapeutic composition that comprises a pharmaceutical formulation of a pharmaceutically acceptable carrier and a human or genetically-engineered monoclonal antibody or antibody binding fragment thereof. The antibody is one that either inhibits aggregation of β -amyloid, maintains the solubility of soluble β -amyloid, or disaggregates an aggregate of β -amyloid. When the antibody is one that inhibits aggregation of β -amyloid or maintains the solubility of soluble β -amyloid, it does so at least to the extent that monoclonal antibody AMY-33 does so. The genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody that either recognizes an epitope within residues 1-28 of β -amyloid or is obtainable using a peptide consisting of residues 1-28 of β -amyloid as an immunogen. The human monoclonal antibody must be one that is obtainable using a peptide consisting of residues 1-28 of β -amyloid as an immunogen. The invention also relates to a method for making such a pharmaceutical formulation by first selecting the

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monoclonal antibody and then genetically engineering it prior to incorporating it into a pharmaceutical formulation.

Copy of Claims in Conventional Amended Format

MPEP §1453.V.D. states with respect to the amendment of new claims:

Although the presentation of the amended claim does not contain any indication of what is changed from the previous version of the claim, applicant must point out what is changed in the "Remarks" portion of the amendment.

Claim 177 has not been amended by the present amendment. All of claims 210-214 are previously presented new claims in the sense that they were not present in the patent as issued and are being amended by the present amendment. Claims 215-228 are new claims. So that the examiner can see how the claims are being amended from the previous version of these claims, the following is a recitation of all of the pending claims, including the three amended claims, shown in the conventional amended format:

1-176 (Cancelled).

177 (Previously Presented). The therapeutic composition of claim 210 or 211, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

178-209 (Cancelled).

210 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the genetically-engineered antibody of (a) that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and

(ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen ~~or recognizes an epitope within residues 1-28 of beta-amyloid;~~ and

wherein said antibody or fragment is not conjugated with a detectable moiety.

211 (Currently Amended). The therapeutic composition of claim 210, wherein said genetically-engineered antibody of (2)(a) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to

an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and said monoclonal antibody is obtainable using a peptide consisting of residues 1-28 of human beta-amyloid as an immunogen~~or recognizes an epitope within residues 1-28 of human beta-amyloid.~~

212 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the human monoclonal antibody of (a) that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said human monoclonal antibody is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen.

213 (Currently amended). The therapeutic composition of claim 212, wherein said human monoclonal antibody of (2)(a) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and wherein said human monoclonal antibody of (a) is obtainable using a peptide consisting of residues 1-28 of human beta-amyloid as an immunogen.

214 (Currently Amended). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a), which fragment inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen ~~or recognizes an epitope within residues 1-28 of beta-amyloid;~~

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

215 (New). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the genetically-engineered antibody of (a) that inhibits aggregation of beta-amyloid or

maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

216 (New). The therapeutic composition of claim 215, wherein said genetically-engineered antibody of (2)(a) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and said monoclonal antibody recognizes an epitope within residues 1-28 of human beta-amyloid.

217 (New). The therapeutic composition of claim 215 or 216, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

218 (New). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2) (a) a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a), which fragment inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and
(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment inhibits aggregation of beta-amyloid or maintains the

solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

219 (New). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that disaggregates an aggregate of β -amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that disaggregates an aggregate of β -amyloid,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) disaggregates an aggregate of β -amyloid and

(ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

220 (New). The therapeutic composition of claim 219, wherein said genetically-engineered antibody of (2)(a) disaggregates an aggregate of human β -amyloid, or said fragment of (2)(b) disaggregates an aggregate of human β -amyloid, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that disaggregates an aggregate of human

β -amyloid and said monoclonal antibody is obtainable using a peptide consisting of residues 1-28 of human beta-amyloid as an immunogen.

221 (New). The therapeutic composition of claim 219 or 220, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

222 (New). A therapeutic composition, comprising:
a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that
disaggregates an aggregate of β -amyloid, or

(b) a fragment of the human monoclonal antibody
of (a) that disaggregates an aggregate of β -amyloid,

wherein said human monoclonal antibody is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen.

223 (New). The therapeutic composition of claim 222, wherein said human monoclonal antibody of (2)(a) disaggregates an aggregate of human β -amyloid, or said fragment of (2)(b) disaggregates an aggregate of human β -amyloid, and wherein said human monoclonal antibody of (a) is obtainable using a peptide consisting of residues 1-28 of human beta-amyloid as an immunogen.

224 (New). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that disaggregates an aggregate of β -amyloid, or (b) a fragment of

the genetically-engineered antibody of (a), which fragment disaggregates an aggregate of β -amyloid, said method comprising:

selecting a monoclonal antibody that

(i) disaggregates an aggregate of β -amyloid,

and

(ii) is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that disaggregates an aggregate of β -amyloid, or a fragment of a genetically engineered antibody, which fragment disaggregates an aggregate of β -amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

225 (New). A therapeutic composition, comprising:
a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2) (a) a genetically-engineered antibody that
disaggregates an aggregate of β -amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that disaggregates an aggregate of β -amyloid,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) disaggregates an aggregate of β -amyloid and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

226 (New). The therapeutic composition of claim 225, wherein said genetically-engineered antibody of (2)(a) disaggregates an aggregate of human β -amyloid, or said fragment of (2)(b) disaggregates an aggregate of human β -amyloid, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that disaggregates an aggregate of human β -amyloid and said monoclonal antibody recognizes an epitope within residues 1-28 of human beta-amyloid.

227 (New). The therapeutic composition of claim 225 or 226, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

228 (New). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that disaggregates an aggregate of β -amyloid, or (b) a fragment of the genetically-engineered antibody of (a), which fragment disaggregates an aggregate of β -amyloid, said method comprising:

selecting a monoclonal antibody that

(i) disaggregates an aggregate of β -amyloid,
and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that disaggregates an aggregate of β -amyloid, or a fragment of a genetically engineered antibody, which fragment disaggregates an aggregate of β -amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

Continuing Obligations

It is noted that the examiner has reminded applicant and applicant acknowledges the continuing obligation under 37 CFR 1.178(b) to timely apprise the Office of any prior or concurrent proceeding in which patent no. 5,688,651 is or was involved, and the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information that is material to patentability of the claims under consideration in the reissue application.

Written Description Rejection

Claims 177, 210-214 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the phrase "genetically-engineered antibodies" is given its

broadest reasonable interpretation and is broad enough to encompass humanized, chimeric, veneered, resurfaced, CDR-grafted and other such engineered antibodies. The examiner states that even claims 177, limited to single chain antibodies, and 212-213, drawn to human monoclonal antibodies, are claims which encompass a genus of antibody molecules differing in structure and epitope specificity. The examiner states that to provide evidence of possession of a claim the genus of the specification must provide sufficient distinguishing identifying characteristics of the genus. The examiner states that the specification contains no indication of the particular structural or physical properties of the claimed antibodies or of any structure/function correlation. The examiner states that apart from a method step to select for antibodies displaying the particular desired functional characteristics, there is no indication of any specific structural properties required for making the claim to genetically-engineered antibody nor is there any identification of any particular portion of the antibody that must be conserved. Accordingly, the examiner concludes that the full breath of the claims does not meet the written description provision of 35 U.S.C. §112, first paragraph. This rejection is respectfully traversed.

The Written Description Training Materials, Revision 1, March 25, 2008, available on the PTO website, has a specific example relating to antibodies against a single protein. This is Example 13, which discusses written

description support for a claim drawn to "an isolated antibody capable of binding to antigen X." In this example, the specification discloses antigen X and discusses antibodies which specifically bind to antigen X but has no working or detailed prophetic example of an antibody that binds to antigen X. The training materials analyze this situation, at pages 45 and 46, as follows:

The specification does not describe an actual reduction to practice of an antibody that binds to antigen X by reference to a deposit (e.g., deposit of a hybridoma) or by describing an antibody in structural terms sufficient to show possession. The specification also does not describe the complete structure of an antibody capable of binding antigen X in detailed drawings or through a structural chemical formula. The specification does not describe a partial structure of the claimed antibody. The specification does not describe any physical or chemical properties of the claimed antibody (e.g., molecular weight, association constant).

The specification does not disclose a correlation between the function of binding to antigen X and the structure of the claimed antibody. Finally, the specification does not describe a method of making an antibody that binds antigen X.

However, the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional.

Antibodies were known to be of five general types; each of the five types had been characterized as having substantial

common structural, chemical and biological features.

The antigen-specific variable regions of antibodies vary.

It does not appear that persons of skill in the art consider knowledge of the amino acid sequence of the variable regions critical for purposes of assessing possession of an antibody.

Considering the facts, including the routine art-recognized method of making antigen-specific antibodies, the adequate description of antigen X, the well-defined structural characteristics for the classes, subclasses and isotypes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology was well developed and mature, one of skill in the art would have recognized that the disclosure of the adequately described antigen X put the applicant in possession of antibodies which bind to antigen X.

Accordingly, the example concluded that the specification satisfied the written description requirement with respect to the full scope of claim 1. These training materials were formally acknowledged and given judicial notice by the Federal Circuit in *Enzo Biochem Inc. v. GenProbe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002).

The present claims are supported in the manner required by the written description requirement of 35 USC 112 for reasons similar to those set forth in the above example. The present specification includes at least one example of the claimed antibody, which is more than the specification had in the above example. The examiner makes much of the fact that

the present claims are "genus" claims that encompass a genus of antibody molecules differing in structure and epitope specificity. But the same is true for the claim being analyzed in Example 13 of the training materials. The antibody could be specific to any epitope on the protein designated as antigen X and each of the antibodies would differ in structure. Obviously, this is not a substantive difference between the present situation and the claim of Example 13. The fact remains that the level of skill and knowledge in the art of antibodies at the time of filing (note that the art relied on for this fact in the training materials was dated in 1976) was such that the production of antibodies against a well-characterized antigen was conventional. The knowledge of the amino acid sequence of the variable regions is not critical for purposes of assessing possession of the antibody. The art is well aware of the well-defined structural characteristics for the classes, subclasses and isotypes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology was well developed and mature.

The present claims differ from the claim of Example 13 in that it is narrower than the recitation of antibodies in Example 13. The present claims do not cover every antibody that is specific to an epitope within 1-28 of A β , but requires another screen of the selected antibodies to select only those that inhibit A β aggregation or cause disaggregation of A β aggregates. However, the fact that the claim is narrower does

not make it lose written description support. The specification discloses that such selection is necessary. An example of one antibody within the scope of the claims is given. Antibody technology is still well developed and mature and the further screen is routine. Thus, the subgenus of the present claims is supported for the same reason that the genus of Example 13 is supported.

Accordingly, in view of the disclosure of the antigen to which the antibody is specific, as well as the disclosure of certain additional screens which must be run in order to make sure that the antibody obtained has all of the claimed properties, and further in view of the well known structure-function relationship of antibody to antigen, one of ordinary skill in the art would understand that the inventor was in possession of the claimed genus.

To the extent that the rejection is also based on the breadth of the term "genetically engineered antibody," the incorporation by reference of publications such as Haber, 1992 (of record in this case) establishes that those of ordinary skill in the art would understand that applicant was in possession of various types of genetically engineered antibodies. The examiner does not contend that the specification is non-enabling, only that the inventor was not in possession of a sufficient number of species to establish possession of the genus. Once one of ordinary skill in the well-developed and mature antibody art is in possession of a monoclonal antibody with certain properties, it is a routine

matter to genetically engineer it to obtain a single-chain, humanized, etc., antibody that maintains the binding characteristics of the starting monoclonal. Thus, the present applicants were in possession of the entire genus of genetically engineered antibodies for the same reason that Example 13 holds that they were in possession of the genus of monoclonal antibodies.

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

Obviousness Rejection over Bickel, Solomon and Ladner

Claims 177, 210 and 211 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bickel as evidenced by Solomon 2002 and in view of Ladner. The examiner states that Bickel teaches the development and characterization of monoclonal antibody AMY-33 which was produced by immunizing animals with residues 1-28 of human beta-amyloid. The examiner states that Bickel discloses the use of AMY-33 diluted in Tris-buffered saline, which meets the limitation of a pharmaceutically acceptable carrier. The examiner states that Bickel suggests that highly specific anti- β -amyloid monoclonal antibodies could be used for such *in vivo* diagnostic methods. The examiner states that AMY-33 inherently inhibits aggregation and/or maintains the solubility of soluble β -amyloid, as it is the same antibody as mentioned in the specification. The examiner recognizes that Bickel does not teach a genetically modified antibody. The

examiner states that Ladner teaches the production of single chain antibodies and further discloses that they may be used for essentially any use that the prior art has envisioned for monoclonal antibodies. The examiner considers that it would have been obvious to genetically-engineer the monoclonal antibody taught by Bickel to make a single chain antibody as taught by Lander with a reasonable expectation of success in producing a molecule with reduced immunogenicity and improved affinity sensitivity, greater stability and reduced cost of production compared to whole antibodies with reasonable expectations of success. The examiner states that motivation to do so is provided by Bickel which states that genetically-engineering the antibody may facilitate the antibodies as neurodiagnostic or therapeutic agents in humans. This rejection is respectfully traversed.

As the examiner recognizes, the only specific utility taught by Bickel is a diagnostic utility. For a diagnostic utility, the antibody must be conjugated to a detectable moiety, such as a fluorescent, metallic, enzymatic or radioactive marker. Bickel does not suggest or enable any use for which such a marker would not be necessary.

In order to avoid this rejection, the genetically-engineered antibody claims have now been amended to specify that the antibody or fragment is not conjugated with a detectable moiety. This is supported by the present specification for the reasons discussed in the statements under 37 CFR §1.173(c), above.

Accordingly, regardless of whether or not Ladner actually suggests the use of single chain antibodies for diagnostic purposes, the presently claimed composition cannot be used for a diagnostic purpose as it excludes antibodies that have a detectable marker. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Obviousness Rejection over Majocha, Solomon and Boerner

Claims 212 and 213 have been rejected under 35 USC §103(a) as being unpatentable over Majocha as evidenced by Solomon 2002, and in view of Boerner. The examiner states that Majocha teaches the use of the residues 1-28 of human beta-amyloid as an immunogen to generate antibodies and that these can be used for diagnostic purposes by detectably labeling them. The examiner states that antibodies raised against the first 28 amino acids of β -amyloid intrinsically have anti-aggregating properties, including solubilization of existing β -amyloid aggregates and inhibition of β -amyloid aggregation, as evidenced by Solomon 2002. Thus, the examiner states that, while Majocha is silent with respect to the functional properties of monoclonal antibodies obtained using A β 1-28 as an immunogen, such inhibitory properties would necessarily be present in these antibodies as evidenced by Solomon 2002. The examiner notes that however Majocha does not teach that the antibodies are human monoclonal antibodies. The examiner states that Boerner teach methods for producing antigen-specific, high-affinity human monoclonal antibodies

which can serve as diagnostic tools to identify the presence of an antigen specific to a disease state. The examiner considers that it would have been obvious to make a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a human monoclonal antibody using A β 1-28 as an immunogen with predictable results and such a composition would be valuable for diagnosis of Alzheimer's disease. This rejection is respectfully traversed.

First of all, both Majocha and Boerner disclose that the only use for such antibodies is for diagnostic purposes. The present claims exclude conjugation with a detectable marker and therefore the composition of the present invention cannot be used for diagnostic purposes. Accordingly, this rejection must be withdrawn for the reasons discussed above with respect to the rejection over Bickel in view of Ladner.

Additionally, Majocha is directed to antibodies that can be used for imaging and diagnosis, which antibodies recognize an epitope within the region of A β 1-28. However, Majocha does not teach that such antibodies will inhibit aggregation of soluble β -amyloid or cause disaggregation of amyloid plaque. It is the examiner's position that all antibodies raised against the first 28 amino acids of β -amyloid will intrinsically have anti-aggregation properties, including solubilization of existing β -amyloid aggregates and inhibition of β -amyloid aggregation. The examiner relies on Solomon 2002 to support this. However, this is simply not the case. Thus, the examiner's conclusion that the compound being

administered in Majocha is the same as that being administered in the present claims is erroneous.

In this regard, the examiner's attention is invited to MPEP 2164.05(a)IV "EXAMINER MUST PROVIDE RATIONALE OR EVIDENCE TENDING TO SHOW INHERENCY," which states in pertinent part:

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)

Thus, in order for such an inherency rejection to be maintained, the examiner must establish that all antibodies raised against A β 1-28 as an immunogen must necessarily prevent aggregation or cause disaggregation of A β .

Those of ordinary skill in the art aware of the literature that has been published on this subject to date are well aware that this conclusion of the examiner is erroneous.

First of all, the present specification clearly states that the antibodies having the desired properties have to be selected (see, for example, at column 5, lines 23-24 and column 6, line 9). The example shows that while AMY-33, which is raised against the 1-28 fragment of A β , inhibits β -amyloid aggregation, monoclonal antibody 6F/3D, recognizing an epitope located between the residues 8-17 of the β -amyloid, does not work.

Furthermore, attached hereto is a Table listing all of the antibodies that have been tested in the literature for either prevention of aggregation of β -amyloid *in vitro*, disaggregation of β -amyloid *in vitro* or *ex vivo*, or disaggregation of β -amyloid *in vivo*. It can be seen that while AMY-33 and eight other antibodies that bind to an epitope between residues 1 and 7 of β -amyloid have shown positive results, one antibody having an epitope of 1-7 had negative results, one that had an epitope of 4-10 had negative results and all of the antibodies having epitopes between 10 and 28 (six other antibodies) showed negative results. Furthermore, three antibodies directed to an epitope between 33 and 42 showed negative results. The publications from which these results were culled are also submitted herewith even though many are already of record in the case.

These results prove that the bold statement that all antibodies that recognize an epitope between 1-28 of A β will prevent aggregation of β -amyloid or will cause aggregated β -amyloid to disaggregate, is unsupportable and untrue. The

Solomon 2002 reference was cited by the examiner to support her conclusion that all antibodies raised against A β 1-28 will yield antibodies that prevent amyloid formation or cause disaggregation. However, a closer reading of this reference teaches just the opposite. The antibodies must be directed to a "strategic" position on the antigen molecule. See page 908, second column, at the end of the first partial paragraph, where it states:

For such an active role, mAbs require a high binding constant to the 'strategic' positions on the antigen molecule.

See also the first full paragraph on page 910 where this publication states:

Disaggregation, as well as the prevention of amyloid formation, was found to be dependent on the location of the epitopes on the A β and on the binding characteristics of the respective antibodies.

Using the phage-peptide libraries, composed of filamentous phage displaying random combinatorial peptides, the author defined the EFRH residues located at positions 3-6 of the N-terminal A β P as the epitope of anti-aggregating antibodies 6C6 and 10D5 within A β P. ... The mAb 2H3, which did not affect A β formation, despite the fact that it binds to the N-terminal of A β P, highlights the importance of this specific sequence region on the behavior of the whole A β P molecule.

Thus, far from disclosing that antibodies raised against the first 28 amino acids of β -amyloid must intrinsically have

anti-aggregating properties, including solubilization of existing amyloid β aggregates and inhibition of amyloid β aggregation, Solomon evidences quite the opposite. A very specific epitope within 1-28 is required, as evidenced by the fact that mAb 2H3 does not affect A β formation. It should be noted that mAb 2H3 appears on the attached Table, which Table supports applicant's position that all of the antibodies of Majocha will not inherently have the ability of inhibiting amyloid formation or causing disaggregation.

The attached Table and accompanying arguments were previously presented during the prosecution of application 11/358,951, which is a reissue application that is a divisional of the present application. In response to this Table and these arguments, the present examiner, in an official action issued in the divisional application, stated that the claims do not require that the prior art antibodies prevent aggregation but only that they inhibit aggregation and thus even a small amount of inhibition would meet the claim limitations. Thus, the examiner concluded that it is reasonably likely that the antibodies taught by Majocha do indeed inhibit β -amyloid aggregation to some extent.

In order to avoid this unintended reading of the claims, which includes negligible amounts of inhibition, the present claims have now been amended to recite that the antibody must inhibit aggregation of β -amyloid or maintain the solubility of soluble β -amyloid "to an extent at least as great as that obtainable with the antibody AMY-33." All of

the antibodies in the Table that are indicated as being negative in inhibition of aggregation of β -amyloid, all have substantially less inhibition than is achieved by AMY-33. Thus, the present claims no longer read on the negligible amounts of inhibition that may be shown for such antibodies. The statements under 37 CFR 1.173(c) hereinabove establish why this new recitation in the claim is supported by the specification. Thus, the present claims now only read on antibodies that have a substantial amount of inhibiting activity.

In addition, new claims 219-228 all now require that the antibody disaggregate an aggregated β -amyloid. This activity is even more selective than inhibition of amyloid aggregation. Accordingly, these claims should be considered separately and are independently free of this rejection.

Accordingly, it would not have been obvious to select from the large genus of antibodies that could be raised by the process of Majocha, only that subclass of antibodies that can be raised using A β 1-28 as an immunogen that will prevent aggregation of β -amyloid or cause disaggregation of β -amyloid aggregate. Majocha does not teach or suggest that subclass. Boerner adds nothing to the deficiencies of Majocha with respect to the identity of antibodies that will inhibit aggregation or cause disaggregation. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Obviousness Rejection over Becker, Cordell Spillantini and Kirschner

Claims 177 and 210-214 have been rejected under 35 USC §103(a) as being unpatentable over Becker in view of Cordell and Spillantini as evidenced by Kirschner. The examiner states that Becker teaches a series of assays for evaluating the efficacy of agents which inhibit the neurotoxic effects of β -amyloid peptide, using β -amyloid peptides that have adopted a secondary structure predominantly of the β -sheet conformation. The examiner states that Becker teaches that β -amyloid protein, which is the main aggregated molecule found in the amyloid plaques of the brains of Alzheimer's disease patients, is toxic to neurons and that there is a direct correlation between the degree of β -sheet structure in the β -amyloid peptide and its neurotoxicity. The examiner states that Becker notes that the neurotoxicity assays can be supplemented by the incubation of β -amyloid peptides which have adopted a predominantly β -sheet conformation with potential inhibitors of neurotoxicity, such that a reduction in neurotoxicity indicates a candidate inhibitor agent. The examiner states that Becker discloses conformationally-specific antibodies and antibody fragments which bind to β -amyloid peptides in a secondary structure-specific manner, as examples of such inhibitory agents. More specifically, the examiner refers to Becker's reference to antibodies that demonstrate specificity for β -sheet in conformation, for use in diagnostics, therapeutics, and/or in diagnostic/therapeutic combinations. The examiner states that Becker teaches that

the disclosed antibodies may be monoclonal, single chain, or genetically-engineered monoclonal antibodies. The examiner states that the teachings of Becker are echoed by Cordell with respect to the inhibition of specific β -amyloid peptide species as a therapy for Alzheimer's disease. The examiner states that Cordell notes that adoption of a β -sheet structure of β -amyloid protein is a requirement for aggregation and insolubility. The examiner states that Cordell discloses that compounds that bind β -amyloid and block its ability to seed further molecular addition would be of therapeutic advantage. The examiner states Becker and Cordell corroborate the need for the production of therapeutic formulations, comprising genetically-engineered antibodies that specifically bind to and inhibit the aggregation of β -amyloid peptide for the treatment of Alzheimer's disease. The examiner recognizes, however, that neither Becker nor Cordell explicitly teach any such antibody or that such an antibody is obtainable using a peptide consisting of residues 1-28 of β -amyloid as an immunogen or is one which recognizes an epitope within residues 1-28 of β -amyloid. The examiner states that Spillantini discloses the different configurational states of β -amyloid and their distributions relative to plaques and tangles in Alzheimer's disease. The examiner states that Spillantini demonstrates that the antibody BR88, raised against residues 1-12 of β -amyloid, labels a large number of tangle-bearing cells, but only a small number of diffuse amyloid deposits, whereas monoclonal antibody 4G8, raised

against residues 17-24 of β -amyloid, stained a large number of diffuse amyloid deposits and plaques in tissue sections from Alzheimer's disease brains. Thus, the examiner states that Spillantini suggests that the epitopes for BR88 and 4G8 are hidden in plaque cores whereas it is accessible in diffuse amyloid deposits and amyloid plaques. The examiner states that Kirschner evidences that the N-terminal region of β -amyloid and in particular the region of residues 1-28 is crucial for β -sheet fibril formation and subsequent aggregation of β -amyloid peptide. Thus the examiner considers the teachings of Spillantini and Kirschner make clear to the artisan of ordinary skill in the art that epitopes on the N-terminal portion of β -amyloid are available to antibodies only when the β -amyloid peptide has not yet densely aggregated into solid core deposits and the region comprising residues 14-28 of β -amyloid is necessary for the aggregation of β -amyloid. Thus, the examiner concludes that one of ordinary skill in the art would have recognized the therapeutic importance of β -amyloid 1-28, and in particular residues 14-28, as a potential target region for agents to reduce and/or block the formation of β -amyloid peptide fibrils before they aggregate and form dense core deposits. The examiner states that the methods taught by Becker et al. would have enabled the ordinarily skilled artisan to select for such inhibitory monoclonal antibodies, genetically-engineer them such that they have reduced immunogenicity (such as single chain antibodies), and subsequently use them in a therapeutic method for the

treatment of Alzheimer's disease. This rejection is respectfully traversed.

Becker at column 5, lines 37-41, suggests that potential inhibitors of neurotoxicity can be found by incubating such potential inhibitors with the β -amyloid peptide in the neurotoxicity assays disclosed. However, nowhere in Becker is it specifically stated that the antibody embodiment of his invention may be used as potential inhibitors of neurotoxicity. Indeed, the next paragraph of Becker, at column 5, beginning at line 42, refers to "another embodiment" of the invention that relates to conformationally specific antibodies. Even the claims of Becker have assay claims for finding potential inhibitors and conformationally specific antibody claims, but nothing to suggest that those conformationally specific antibodies would be potential inhibitors of neurotoxicity.

Furthermore, Becker speaks of two different types of specific antibodies that may be useful in treating Alzheimer's disease. The first are antibodies that bind only those β -amyloid peptides which are predominantly in a β -sheet conformation. The second set of antibodies binds only those β -amyloid peptides that have adopted a random coil or α -helix conformation. See column 5, lines 42-50, and column 7, lines 26-38, of Becker. The paragraph at column 8, lines 16-18, indicating that the "antibodies of the present invention" are useful in the treatment of mammals suffering from Alzheimer's

disease, does not suggest what antibodies might be useful for this purpose or how they might be useful.

As the examiner recognizes, Becker does not teach any particular antibody. Becker is only hypothesizing that such antibodies might exist and be useful without even indicating how or why they might be useful or what epitopes might be useful. These deficiencies in Becker are not supplied by Cordell, Spillantini or Kirschner. Cordell teaches that β -sheet structure is a requirement for aggregation and insolubility, as noted by the examiner. However, Cordell also teaches at page 80, last three lines:

The hydrophobic carboxyl-terminal portion of the β -amyloid molecule is critical in establishing aggregates.

Cordell does not teach that antibodies against any region of A β might be useful in preventing aggregation or causing disaggregation. It only talks of mechanisms of β -sheet formation. It does not suggest that antibodies can be used for this purpose or which antibodies or how to find them.

Spillantini teaches nothing whatsoever about any potential use for antibodies against β -amyloid. As stated in the first paragraph of the discussion on page 3949, Spillantini's study only demonstrates that antisera against peptides in β -amyloid can be obtained that react predominantly with one of a number of different objects - namely amyloid plaques without cores, amyloid plaques with cores or tangled bearing bodies and cells. In the last paragraph on page 3951,

Spillantini states that much can be gained by using different anti- β -amyloid antisera in trying to access the amyloid pathology of Alzheimer's disease. However, there is nothing in Spillantini to suggest that any of the three antibodies used in his analysis might possibly inhibit aggregation or cause disaggregation.

Similarly, Kirschner relates only to studies of β -amyloid aggregation and the examiner states that Kirschner teaches that the region comprising the residues 18-28 is crucial for β -sheet fibril formation and subsequent aggregation beta-amyloid peptide. Again, however, these theoretical considerations have nothing whatsoever to do with any suggestion that any particular antibody against β -amyloid will prevent aggregation or cause disaggregation of β -amyloid plaques.

Clearly, this is an attempt at a hindsight reconstruction of the present invention. The Federal Circuit stated *In re Fritch*, 23USPQ2d 1780, 1784 (Fed. Cir. 1992):

Here, the examiner relied upon hindsight to arrive at the determination of obviousness. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. [footnotes omitted]

The recent Supreme Court decision of *KSR Int'l Co. v. Teleflex Inc.*, 550 US 398, 421, 82 USPQ2d 1385, 1397 (2007) confirms this law where it states states:

A factfinder should be aware, of course, of the distortion by hindsight bias and must be cautious of arguments relying upon *ex post* reasoning.

It appears that the examiner is taking the position that it would be obvious-to-try antibodies raised against 1-28 and particularly 14-28 of A β to see if they will inhibit neurotoxicity or perhaps to otherwise see if they have the properties required of the antibodies of Becker. *KSR* indicates that the "obvious-to-try" standard only applies when there are a finite number of identified, predictable solutions. Note *KSR*'s analysis of obvious-to-try where it states, 550 US at 421, 82 USPQ2d at 1390:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his/her technical grasp.

This statement of the Supreme Court has recently been analyzed by the Federal Circuit in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, 87 USPQ2d 1450 (Fed. Cir. 2008). Citing this portion of *KSR*, the court stated that 1457:

To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle

because potential solutions are less likely to be genuinely predictable.

There is certainly no finite number of predictable solutions of how to find an antibody that will inhibit neurotoxicity in accordance with Becker. There are not a finite number of antibodies to be tested. Furthermore, it would not be expected that all antibodies recognizing an epitope within A β 1-28 would have such properties. This is demonstrated by the results in the present specification where AMY-33 works and antibody 6F/3D, raised against peptides 8-17 of the β -amyloid did not work. See Example 2, beginning at page 15 of the present specification. Furthermore, the attached Table shows that screening is necessary to find the antibodies that work, confirming the statements made in the present specification. Furthermore, even if one were to try antibodies against 14-28, these would fail, as demonstrated in the attached table which indicates that an antibodies against 13-28, 16-24 and 18-21 are all negative in disaggregating and/or prevention of aggregation.

For all of these reasons one of ordinary skill in the art would not have found it obvious from a reading of the four references relied upon the examiner to find a human antibody or to genetically engineer an antibody that is obtainable using a peptide consisting of residues 1-28 of β -amyloid immunogen which recognizes an epitope within residues 1-28 of β -amyloid and which antibody has the property of inhibiting aggregation of β -amyloid or maintaining the solubility of soluble β -amyloid to an extent at least as great

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as obtainable with antibody AMY-33 or to disaggregate β -amyloid. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Conclusion

It is submitted that all of the claims now present in case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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TABLE

Antibody	Immunogen	Epitope	Disaggregate <i>In vivo</i>	Disaggregate <i>In vitro</i> or <i>Ex vivo</i>	Prevention of Aggregation <i>In Vitro</i>
AMY-33	1-28 ⁶	?			+ ^{2, 6}
6C6	1-28 ⁵	3-7 ⁵		+ ^{5, 7}	+ ^{2, 7, 8, 10}
10D5	1-28 ⁵	3-6 ¹¹	+ ^{1, 3}	+ ^{5, 11}	+ ^{2, 8, 10}
3D6	1-5 ⁴	1-5 ¹¹	+ ³	+ ^{5, 11}	
12B4	1-42 ⁵	3-7 ⁵		+ ⁵	
2C1	1-42 ⁵	3-7 ⁵		+ ⁵	
12A11	1-42 ⁵	3-7 ⁵		+ ⁵	
3A3	1-42 ⁵	3-7 ⁵		+ ⁵	
22C8		3-7 ¹¹		+ ¹¹	
2H3	1-12 ⁴	1-7 ¹⁰			— ^{2, 8, 10}
6E10		5-10 ¹¹		— ¹¹	
14A8		4-10 ¹¹		— ¹¹	
18G11		10-18		— ¹¹	
1C2	13-28 ⁷	13-28 ⁷		— ⁷	— ^{2, 7, 8}
16C11	23-42 ⁵	23-42 ⁵	— ³	— ^{5, 11}	
266	13-28 ⁴	16-24 ¹¹	— ⁹	— ^{5, 11}	— ⁸
22D12	13-28 ⁵	18-21 ¹¹		— ^{5, 11}	
6F/3D	8-17 ⁶				— ⁶
21F12	33-42 ⁴	33-42 ⁵	— ³	— ^{5, 11}	
14C2		33-40 ⁷		— ⁷	— ⁷
2G3	33-40 ⁴			— ¹¹	

¹ Bacskai et al., "Imaging of Amyloid- β Deposits in Brains of Living Mice Permits Direct Observation of Clearance of Plaques with Immunotherapy", *Nature Medicine*, 7:369-372 (2001)

² Hanan et al., "Inhibitory Effect of Monoclonal Antibodies on Alzheimer's β -Amyloid Peptide Aggregation", *Amyloid: Int. J. Exp. Clin. Invest.*, 3:130-133 (1996)

³ Bard et al., "Peripherally Administered Antibodies Against Amyloid β -Peptide Enter the Central Nervous System and Reduce Pathology in a Mouse Model of Alzheimer Disease", *Nature Medicine*, 6:916-919 (2000)

⁴ Johnson-Wood et al., "Amyloid Precursor Protein Processing and A β ₄₂ Deposition in a Transgenic Mouse Model of Alzheimer Disease", *Proc. Natl. Acad. Sci. USA*, 94:1550-1555 (1997)

⁵ Bard et al., "Epitope and Isotype Specificities of Antibodies to β -Amyloid Peptide for Protection Against Alzheimer's Disease-like Neuropathology", *Proc. Natl. Acad. Sci. USA*, 100:2023-2028 (2003)

⁶ Solomon et al., "Monoclonal Antibodies Inhibit *in vitro* Fibrillar Aggregation of the Alzheimer β -Amyloid Peptide", *Proc. Natl. Acad. Sci. USA*, 93:452-455 (1996)

⁷ Solomon et al., "Disaggregation of Alzheimer β -Amyloid by Site-Directed mAb", *Proc. Natl. Acad. Sci. USA*, 94:4109-4112 (1997)

⁸ Solomon et al., "The Amino Terminus of the β -Amyloid Peptide Contains an Essential Epitope for Maintaining its Solubility", in *Progress in Alzheimer's and Parkinson's Diseases*, Fisher et al., ed., Plenum Press, New York, 205-211 (1998)

⁹ DeMattos et al., "Peripheral Anti-A β Antibody Alters CNS and Plasma A β Clearance and Decreases Brain A β Burden in a Mouse Model of Alzheimer's Disease", *Proc. Natl. Acad. Sci. USA*, 98:88-50-8855 (2001)

¹⁰ Frenkel et al., "High Affinity Binding of Monoclonal Antibodies to the Sequential Epitope EFRH of β -Amyloid Peptide is Essential for Modulation of Fibrillar Aggregation", *Journal of Neuroimmunology*, 95:136-142 (1999)

¹¹ Schenk., US 6,761,888 – Table 16 (col 63)